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THE SPECIFICITY OF THE DESENSITIZED STATE IN SERUM ANAPHYLAXIS *

HOWARD T. KARSNER AND ENRIQUE E. ECKER

From the Department of Pathology, School of Medicine, Western Reserve University, Cleveland, Ohio

Aside from the academic questions involved, there is an important practical problem which concerns the specificity of the desensitized state in anaphylaxis. If the occasional hypersensitiveness of man to serums which contain specific immune substances could be reduced or eliminated, the safety of employment of such serums would be much enhanced. The danger of specific desensitization lies largely in the possibility of severe or even fatal shock during desensitization. Nonspecific desensitization might eliminate this danger. Although there are certain hypersensitive states to pure or relatively pure proteins, as for example, those of the vegetable pollens, the fatalities in man have so far resulted from injections of serum. We have therefore confined this study to serum anaphylaxis in the hope that ultimately a practical method may be devised for employment in man. It does not necessarily follow that results in animals, which have been artificially sensitized, are entirely applicable to natural hypersensitiveness in man, but there are instances of the acquired state in man which seem to be identical with that of animals and it has yet to be proved that natural hypersusceptibility differs materially. If, therefore, nonspecific desensitization in the acquired serum hypersusceptibility of animals can be demonstrated satisfactorily it is worthy of further trial in human experiments.

Most studies of anaphylaxis have dealt with serum anaphylaxis and the same is true of the desensitized state. The specificity of the desensitized state has been supported by the work of Otto,[1] Rosenau and Anderson,[2] Szymanowsky,[3] Kumagai and Odaira,[4] and in particular by Besredka.[5] Nonspecific, usually transitory, reduction of shock has been produced by the injection of various substances, but the final issue as regards specificity of this phenomenon is still a matter of considerable dispute. Biedl and Kraus[6] assert

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[1] München. med. Wchnschr., 1907, 54, p. 1665.

[2] Hyg. Lab., Bull. 29, 1906; Bull. 45, 1908.

[3] Ztschr. f. Immunitätsf. u. Exper. Therap., 1917, 26, p. 213.

[4] Ztschr. f. Immunitätsf. u. Exper. Therap., 1912, 14, p. 391.

[5] Anaphylaxie et Antianaphylaxie, 1917.

[6] Wien. klin. Wchnschr., 1909, 22, p. 363.

that animals sensitized to serums can be desensitized with heterologous substances such as peptone, but Besredka[5] was unable to confirm their work. Kopaczevski and Vohram[7] found that sodium oleate reduces anaphylactic shock, which they assert is due to a lowering of surface tension of the blood. Even such a salt as sodium chloride has been employed with some degree of success. Richet[8] ascribes the action of this salt to a distinct influence on the nerve cells, while other investigators attribute its effect to a modification of the colloidal state of fluids and cells. Pfeiffer and Mita[9] protected sensitized animals against lethal doses of the homologous serum (horse) by previous injections of beef serum. Weil[10] desensitized guinea-pigs, passively sensitized to horse serum, with rabbit serum. More recently Calvary,[11] Bessau,[12] Benjamin and Witzinger,[13] Penna and Moreno, Penna, Cuenca and Kraus,[14] Thomson,[15] Massini[16] and also Brack[17] have examined the subject anew. According to Calvary,[11] it seems that in dogs there is an increase of lymph flow during anaphylactic shock. If, however, previous injections of beef serum are made, such an increase of lymph flow is not demonstrable. Bessau asserts that there is no difference between desensitization with homologous and heterologous serum. Bessau[18] further states that if animals are sensitized to two proteins, anaphylactic shock produced by either protein leads to reduction in the amount of precipitins for both antigens, although the homologous precipitin is the more markedly reduced. Benjamin and Witzinger,[13] who studied the problem in man, came to the conclusion that under certain conditions one antigen may modify the reaction of the other, and these authors called the phenomenon: "La competeneia de antigenos," or "antigenic antagonism." Penna and Moreno[14] were unable to desensitize in man. In animals desensitization can be more readily produced, as is known from the extensive work of Besredka, Alexandrescu and Cinca, and others. Penna, Cuenca and Kraus[14] have shown that serum disease in man is modified or prevented if beef serum is injected before the use of horse serum. Thomson[15] states that much depends on the degree of sensitiveness, that is, the relation between the period of maximal sensitization and the time of desensitization. He refers nonspecific interference in shock to a reduction in the speed of reaction between antigen and antibody whereby a greater amount of the antigen is required to induce shock. The cause of the speed reduction, however, is not explained. Massini,[16] using intestinal segments, concludes that antianaphylaxis is specific, but that there is in addition a nonspecific element. Friedberger refers this phenomenon to an aspecific resistance. Brack, using the method of Massini, found a distinct quantitative difference between specific antianaphylaxis and aspecific antianaphylaxis. The injection of heterologous serum into highly sensitized animals may lead to shock, but the reaction is a great deal less than in the case of the homologous serum. The nonspecific shock may reduce the toxic effects of the homologous serum. Of some bearing on this problem are also the experiments of Lewis,[19] who found that if definite amounts of horse serum are slowly added to dog serum, and injected into guinea-pigs, sensitization to the horse serum is not produced. According to this author, as much as 0.1 c c horse serum in 10 c c of dog serum would not sensitize, even though 0.000,001 c c of horse serum alone will produce a high degree of sensitization. He further found that not only will dog serum inhibit sensitization to horse serum, but other serums (human, cat, beef) will do likewise, and these serums will also inhibit sensitization to dog serum if the proportions are reversed. Further experiments also showed that not only serums but also solutions of pure proteins (egg albumin) in the proper amounts will inhibit sensitization to another protein. Wells[20] claims that experiments with such hopelessly complex mixtures as are furnished by serum, organ extracts, or even egg white and milk, cannot be expected to yield much valuable information concerning specificity. He further states that "if the antigens are isolated proteins, purified as completely as possible, striking illustrations of specificity may be demonstrated both by sensitizing and by desensitizing with specific proteins." Wells' experiments are conclusive in so far as pure proteins are concerned, but the immediate problem as concerns shock in man deals principally with serum anaphylaxis.

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[7] Compt. rend. Acad. d. sc., 1919, 169, p. 250.

[8] Compt. rend. Acad. d. sc., 1919, 169, p. 9.

[9] Ztschr. f. Immunitätsf. u. Exper. Therap., 1910, 4, p. 410.

[10] Ztschr. f. Immunitätsf. u. Exper. Therap., 1914, 20, p. 199.

[11] München. med. Wchnschr., 1911, 58, p. 1442.

[12] Centralbl. f. Bakteriol., I, O., 1911, 60, p. 637.

[13] Ztschr. f. Kinderheilk., 1911, 3, p. 73.

[14] Rev. del Inst. Bakteriol., Dep. Nacional de Hygiene, 1919, 2, p. 1.

[15] Ztschr. f. Immunitätsf. u. Exper. Therap., 1917, 26, p. 213.

[16] Ztschr. f. Immunitätsf. u. Exper. Therap., 1918, 27, p. 194.

[17] Ztschr. f. Immunitätsf. u. Exper. Therap., 1921, 31, p. 407.

[18] Centralbl. f. Bakteriol., 2, O., 1914, 74, p. 162.

METHOD

The experiments were undertaken to study various conditions of nonspecific reduction or elimination of anaphylactic shock. With a variety of heterologous serums we have studied the relative effectiveness of the subcutaneous, intraperitoneal and intravenous routes of injection in desensitization. We have considered the time allowed for absorption by these routes. The type of reaction in shock has been observed in relation to the various serums used for desensitization. Individual variations in animals are recognized as an important factor of error and where essentially toxic serums have been employed, the dosage has been regulated so as to reduce the factor of essential toxicity.

Guinea-pigs have been used throughout. They have been sensitized, in some series intraperitoneally, in others subcutaneously with either horse serum or human serum, or in one series with beef serum. The time allowed for sensitization has varied but in general is about three weeks. Horse, beef, goat, sheep, swine, dog, cat, rabbit and human serums have been employed in desensitization. Desensitization with homologous serums was usually in doses of about 0.05 c c, whereas the dose of heterologous serum varied between 0.5 c c and 2.0 c c. The injections varied from one to four in number and in different series were given subcutaneously, intraperitoneally or intravenously. On the day selected for producing anaphylactic shock, the minimal fatal dose of homologous serum was determined. The delicacy of the determination in our experiment permits a factor of error of 0.05 c c, not considered important in the type and number of experiments performed. Careful necropsies were made on all animals that died.

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[19] Jour. Am. Med. Assn., 1921, 76, p. 1342.

[20] Physiological Reviews, 1921, 1, p. 44.

TABLE 1

THE EFFECT OF SUBCUTANEOUS DESENSITIZATION WITH HOMOLOGOUS AND HETEROLOGOUS SERUMS 24 HOURS PRIOR TO THE TOXIC DOSE *

Animals		Desensitization					Intoxication				
No.	Wt. in Gm.	Date, 1919	Serum Used	Amount Given Subcutaneously Oct. 30		Reaction	Toxic Dose Horse Serum Intravenous	Date, 1919	Hour	Reaction	Necropsy
				A.M.	P.M.						
106	346	10/30	—	—	—	......	0.2	10/31	9:27	9:28, mod. dyspnea; 9:30, hair ruffled; 9:35, on side; 9:47, severe dyspnea; 9:47, dead	Typical
121	375	10/30	Horse	0.05	0.1	—	0.2	10/31	10:00	10:02, convulsion, severe dyspnea; 10:04, hair ruffled	
111	355	10/30	Horse	0.05	0.1	Slight	0.2	10/31	10:22	10:25, rubbed nose and body	
123	377	10/30	Beef	0.5	1.0	—	0.2	10/31	9:49	9:51, mod. dyspnea; 9:54, severe dyspnea, on side; 10:17, dead	Slight distention of lungs
108	330	10/30	Beef	0.5	1.0	—	0.2	10/31	10:16	10:20, mod. dyspnea; 10:24, severe dysp.; 10:26, on side; 10:58, dead	Slight to mod. distention of lungs; slight hemorrhages
118	365	10/30	Hog	0.5	1.0	—	0.2	10/31	9:42	9:45, slight dyspnea; 9:45, rubs nose; 10:04, convulsions; 10:05, dead	Slight distention of lungs
119	355	10/30	Hog	0.5	1.0	—	0.2	10/31	10:10	10:11, convulsions; 10:16, dead	Typical
107	295	10/30	Human	0.5	1.0	—	0.2	10/31	9:33	9:35, mod. dyspnea; 9:38, convulsions; 9:43, dead	Typical
112	275	10/30	Human	0.5	1.0	—	0.2	10/31	9:55	9:57, convulsions; 9:59, dead	Typical

* All animals were sensitized intraperitoneally with 0.05 c c horse serum, Oct. 9, 1919. Desensitizing doses of serums were given in 2 subcutaneous doses 21 days subsequently and the toxic dose intravenously the next day. Note protection by homologous serum and failure on the part of heterologous serums.

EXPERIMENTS

Series 1.—The object of this series was to determine the effect of homologous or heterologous serums given subcutaneously in 2 doses on the day preceding intoxication. With the toxic dose selected, the animal which was not desensitized in any way died in 20 minutes with typical symptoms of shock and typical necropsy findings. Those which were desensitized with homologous serum reacted severely, but survived, while all those that were desensitized with heterologous serums died. The details of this experiment are shown in table 1. The size of the doses employed .in this experiment was determined by preliminary experiments. The series shows that in the doses employed the subcutaneous injection of heterologous serums does not suffice to protect the animal from anaphylactic shock.

TABLE 2

THE EFFECT OF INTRAPERITONEAL DESENSITIZATION WITH HOMOLOGOUS AND HETEROLOGOUS SERUMS 24 HOURS PRIOR TO THE TOXIC DOSE *

Animals		Desensitization				Intoxication				
No.	Wt. in Gm.	Date, 1919	Serum Used	Dose of Serum	Reaction	Toxic Dose Horse Serum Intravenous	Date, 1919	Hour	Reaction	Necropsy
117	334	—	—	—	—	0.2	10/29	9:50	9:54, mod. dyspnea; 9:58, rubbed nose, hair ruffled; 9:59, convulsions; 9:60, dead	Typical
122	330	—	—	—	—	0.2	10/29	10:20	11:22, restless, scratched nose, convulsions; 11:26, dead	Typical
100	278	10/28	Horse	0.05	Distinct	0.2	10/29	10:55	10:58, mod. dyspnea, restless; 11:00, hair ruffled; 11:06, rubbed nose	
101	255	10/28	Horse	0.5 1:1,000	None	0.2	10/29	11:08	11:09, mod. dyspnea; 11:24, on side, very sick	
102	322	10/28	Beef	0.5	None	0.2	10/29	11:00	11:03, mod. dyspnea, convulsions, on side, very sick	
103	265	10/28	Beef	1.0	None	0.2	10/29	11:12	11:15,marked dyspnea, defecation, 11:18, rubbed nose	
104	300	10/28	Swine	0.5	None	0.2	10/29	10:24	10:25, mod. dyspnea; 10:26, rubbed nose; 10:35, hair ruffled, defecation	
105	315	10/28	Swine	1.0	None	0.2	10/29	10:09	10:10, slight dyspnea, hair ruffled 10:14, marked dyspnea; 10:30, convulsions; 10:43, dead	Moderate distention of lungs

* All animals were sensitized intraperitoneally with 0.05 c c horse serum, Oct. 13, 1919. Desensitizing doses of serums were given in single intraperitoneal injections 15 days subsequently and the toxic doses intravenously the next day. Note protection by small dose of horse serum, both doses of beef serum and larger dose of swine serum.

Series 2.—This series was designed to determine the protective effect of intraperitoneal desensitization. The animals were desensitized by a single small dose of homologous horse serum and somewhat larger doses of sheep and of swine serum. The control animals which were not desensitized died typically in respectively 10 and 8 minutes following injection. Those desensitized with homologous serum showed, following the toxic injection, distinct, but not fatal, symptoms of anaphylactic shock. Of those desensitized with sheep serum both were distinctly shocked but survived. Of the two desensitized with swine serum, one died after typical symptoms but at necropsy showed only moderate distention of the lungs. It is therefore apparent that by intraperitoneal injection, and with the amount of serum used, the heterologous serums serve to protect. Even in the case of the animal that died, death was considerably postponed as contrasted with the rapid death of the control animals.

TABLE 3

THE EFFECT OF SUBCUTANEOUS AND INTRAPERITONEAL DESENSITIZATION WITH 4 INJECTIONS OF HOMOLOGOUS OR HETEROLOGOUS SERUMS IN INCREASING AMOUNTS *

Animals		Desensitization							Intoxication			
No.	Wt. in Gm.	Dates and Amounts, 1920				Serum Used	Route of Injection	Reaction	Toxic Dose Horse Serum Intravenous	Nov. 11	Reaction	Necropsy
		Nov. 9		Nov. 10						Hour		
		A.M.	P.M.	A.M.	P.M.							
133	257	—	—	—	—	—	—	—	0.2	9:46	9:48, severe dyspnea; 9:50, convulsions; 9:55, dead	Moderate inflation of lungs
132	270	0.05	0.1	0.2	0.4	Horse	Subcutaneous	—	0.2	9:55	9:57, ha'r ruffled; 9:58, slight dysp.	
131	265	0.05	0.1	0.2	0.4	Horse	Intraperitoneal	—	0.2	9:57	9:59, restless	
127	345	0.1	0.2	0.3	0.4	Swine	Intraperitoneal	—	0.2	9:36	9:39, severe dyspnea; convulsions; 9:43, dead	Moderate inflation of lungs
115	345	0.1	0.2	0.3	0.4	Swine	Subcutaneous	—	0.2	9:43	9:44, rubbed nose; 9:45, hair ruffled; slight dysp.	
128	310	0.1	0.2	0.3	0.4	Beef	Subcutaneous	—	0.2	10:16	10:17, rubbed nose; 10:19, hair ruffled; 10:30, mod. dyspnea	
135	330	0.1	0.2	0.3	0.4	Beef	Intraperitoneal	—	0.2	10:11	10:13, dyspnea; 10:14, rubbed nose; 10:16, convulsions; 10:30, dead	Typical
113	327	0.1	0.2	0.3	0.4	Human	Subcutaneous	..	0.2	9:50	9:53, hair ruffled; 9:54, dyspnea	
129	297	0.1	0.2	0.3	0.4	Human	Intraperitoneal	..	0.2	10:23	10:25, hair ruffled, mod. dyspnea; 10:32, rubbed nose	

* All animals were sensitized intraperitoneally with 0.05 c c horse serum, Oct. 22, 1919. Desensitization, covering 2 days, was begun 18 days subsequently and the toxic doses given the day following the second day of desensitization. Heterologous desensitization is apparent but irregular.

Series 3.—This series was undertaken in order to compare and estimate the result of desensitization intraperitoneally or subcutaneously by means of several injections of homologous or heterologous serums. The animals were all sensitized intraperitoneally and the desensitizing doses were given so that of each pair of animals one was desensitized intraperitoneally and the other subcutaneously. The toxic dose of homologous horse serum killed a pig, which had not been desensitized, in 5 minutes, with typical symptoms and typical necropsy findings. Animals desensitized with homologous serum showed relatively slight symptoms. Of the 6 animals that were desensitized with heterologous serums, 4 survived after fairly severe shock. The two that succumbed following desensitization were desensitized by the intraperitoneal route. We do not interpret this as indicating ineffectiveness of this method, but rather attribute it to individual differences in animals. Table 3 shows the protocol of this series.

Series 4.—In this series the preceding experiment was practically duplicated except that the multiple desensitizing doses were all given subcutaneously and instead of the swine, beef and horse serums we employed goat, dog and rabbit serums. The control animal, not desensitized, died in 5 minutes with typical shock. Those desensitized with homologous horse serum, although severely shocked, survived. Of those desensitized with the heterologous serums, one of each group died following typical symptoms and exhibited at necropsy typical findings. The other three were severely shocked, but survived. It is not considered necessary to submit a protocol of this series, which is essentially the same as the preceding series. It is evident, however, that by fractional desensitization it is possible to protect with homologous serum, and also it is possible to protect in a certain portion of the cases by the use of heterologous serums.

Series 5 and 6.—In these two groups of experiments the animals were desensitized subcutaneously with human serum. In both series desensitization was by the intraperitoneal route. In series 5 a single injection was given and in series 6 two injections were given 24 hours apart. In series 5, with a single desensitizing dose, the homologous human serum failed to protect in doses of 0.1 and 0.2 c c. The heterologous rabbit and horse serums were given in doses of 1 and 2 c c. Of these 5 animals, only 1 survived, namely, that which had 1 c c rabbit serum. The control animals that were not desensitized died in respectively 5 and 7 minutes with typical symptoms and typical necropsy findings. It is probable that the amount of serum used in this experiment was inadequate, but with the doses employed it appears that a single intraperitoneal injection failed to desensitize adequately, either with homologous or heterologous serums. In series VI the same experiment was performed with different serums and with 2 protecting doses. In this series 0.1 c c of the homologous human serum failed to produce fatal shock in the nondesensitized control, whereas 0.2 c c produced death in 7 minutes with typical symptoms and typical necropsy findings. Those animals protected by 2 intraperitoneal doses of homologous human serum showed only moderate symptoms following the toxic dose. Of 3 animals desensitized with ox serum, 2 succumbed, whereas of the 3 desensitized with rabbit serum all survived. It must be noted that the only survival of those desensitized with ox serum, received only one intraperitoneal injection, but in the case of this animal and in the case of that which was desensitized with only one injection of rabbit serum it is important to note that 48 hours elapsed before the toxic dose was given. Details of series 6 are found in table 4. As series 5 is simply a series of fatalities, it is not necessary to append a protocol.

Series 7.—This series was undertaken in order to determine whether there is a quantitative difference in reaction depending on the amount of serum employed for protection. In order to eliminate, in so far as possible, individual differences in absorption of the serum, the intravenous method of desensitization was employed. In desensitizing with homologous serum it was found that reaction occurred in proportion to the amount of serum employed. In spite of the fact that on the day of desensitization 0.05 c c homologous human serum killed the animal in 7 minutes, on the following day when intoxication was performed, 0.2 c c was necessary to obtain a fatal result. Even in the smallest dose for desensitization, protection was sufficient to prevent death, although with this dose the reaction was distinctly more severe than with the larger doses. Desensitization with heterologous serums was practiced with approximately 10 times the amount of homologous serum, and it is seen that the smallest doses of rabbit and horse serum failed to prevent death. The larger doses were effective in preventing death, but the reaction was practically as severe as with the homologous desensitization. Within the limits of the experiment, it is apparent that there is a quantitative difference in effects, depending on the amount of serum used, but this cannot be regarded as definitely proportionate to the amount of serum employed. Table 5 shows the details of this series. It will be noticed that in the amounts of serum employed, intravenous desensitization both with homologous and heterologous serums is highly effective.

TABLE 4

THE EFFECT OF INTRAPERITONEAL DESENSITIZATION WITH 2 INJECTIONS OF HOMOLOGOUS OR HETEROLOGOUS SERUMS *

Animals		Desensitization				Intoxication				
No.	Wt. in Gm.	Serums Used	Dates and Amounts, Intraperitoneal, 1920		Reaction	Toxic Dose Human Serum	Date	Hour, P. M.	Reaction	Necropsy
			Mar. 24	Mar. 25						
73	367	—	—	—	—	0.2	3/26	1:40	1:42, severe dyspnea, hair ruffled, scratched nose; 1:44, convulsions; 1:47, dead	Typical
90	262	—	—	—	—	0.1	3/26	1:49	1:51, scratched nose; 1:54, mod. dyspnea	
85	270	Human	0.1	0.1	—	0.2	3/26	1:57	1:59, scratched nose and body; 1:60, mod. dyspnea	
86	260	Human	0.1	0.1	—	0.2	3/26	2:05	2:08, hair ruffled	
93	315	Ox	1.0	1.0	—	0.2	3/26	2:23	2:24, scratched nose and body, mod. dysp.; 2:25, convulsions, on side; 2:27, dead	Typical
89	322	Ox	1.0	0.5	—	0.2	3/26	2:19	2:20, severe dyspnea, coughed, scratched; 2:22, hair ruffled; 2:24, convulsions; 2:27, dead	Typical
78	352	Ox	1.0	—	—	0.2	3/26	2:09	2:11, scratched nose; 2:12, coughed, hair ruffled	
77	242	Rabbit	1.0	1.0	—	0.2	3/26	2:26	2:28, hair ruffled, slight dyspnea; 2:30, scratched head; 2:33, on side	
87	287	Rabbit	1.0	0.5	—	0.2	3/26	2:30	2:33, slight dyspnea, scratched nose	
42	300	Rabbit	1.0	—	—	0.2	3/26	2:15	2:17, moderate dyspnea, hair ruffled, restless	

* All animals were sensitized subcutaneously with 0.05 c c human serum, March 10, 1920. Desensitizing doses were given 14 and 15 days subsequently and the toxic doses given the next day. Heterologous desensitization was apparent but irregular.

Series 8.—In this series practically an identical experiment was performed except that the animals were sensitized to horse serum. The desensitization was practiced after the height of sensitization had passed, namely 50 days after sensitization. Desensitization was practiced with the homologous horse serum and heterologous sheep and human serum, the latter two in doses approximately 10 times that of the homologous serum. Desensitization was produced by the intravenous route and shock was produced 24 hours later by the same route. The same gradation of desensitizing doses was employed as in the preceding

TABLE 5

THE QUANTITATIVE EFFECT OF INTRAVENOUS DESENSITIZATION WITH HOMOLOGOUS AND HETEROLOGOUS SERUMS *

Animals		Desensitization			Intoxication				
No.	Wt. in Gm.	Serums and Amounts Intravenous, May 4, 1921		Reaction	Toxic Dose Human Serum	Date	Hour	Reaction	Necropsy
141	300	—	—	—	0.1	5/5	10:03	10:05, ruffling of hair, 10:06, mod. dyspnea; restless	
95	290	—	—	—	0.15	5/5	10:22	10:24, coughed; 10:25, hair ruffled, moderate dyspnea, scratched nose	
73	350	—	—	—	0.2	5/5	10:32	10:34, coughed; 10:35, hair ruffled, severe dyspnea, scratched; 10:47, dead	Typical
15	260	Human	0.05	Severe, dead in 7 min.	—	—	—	....	Typical
241	270	Human	0.025	Moderate to severe	0.2	5/5	10:41	10:45, restless; 10:48, hair ruffled, slight dyspnea, scratched nose	
380	275	Human	0.01	Moderate	0.2	5/5	10:48	10:50, scratched nose, moderate dyspnea; 10:57, coughed	
62	300	Human	0.005	Slight	0.2	5/5	10:37	10:40, slight dyspnea	
8	310	Human	0.001	None	0.2	5/5	10:45	10:47, slight to moderate dyspnea, hair ruffled; 10:48, coughed; 10:57, on side, very sick	
161	275	Rabbit	0.5	None	0.2	5/5	11:08	11:10, scratched nose, hair ruffled; 11:13 slight dyspnea	
54	280	Rabbit	0.25	None	0.2	5/5	11:05	11:07, ruffling of hair, scratched nose; 11:08, coughed, mod. dyspnea	
336	300	Rabbit	0.1	None	0.2	5/5	11:00	11:02, slight dyspnea, hair ruffled; 11:04, scratched nose	
42	310	Rabbit	0.05	None	0.2	5/5	—	Unsuccessful injection	
57	325	Rabbit	0.025	None	0.2	5/5	11:05	11:07, hair ruffled, scratched nose; 11:08, coughed, mod. dyspnea 11:12, convulsions; 11:15, dead	Typical
58	280	Horse	0.5	None	0.2	5/5	11:27	11:28, scratched nose mod. dyspnea, very sick	
39	290	Horse	0.25	None	0.2	5/5	11:12	11:14, scratched nose and body	
290	295	Horse	0.1	None	0.2	5/5	11:15	11:16, scratched nose and body, hair ruffled, slight dyspnea	
106	310	Horse	0.05	None	0.2	5/5	11:30	Convulsions; 11:32, hair ruffled, mod. dyspnea, convulsions; 11:35, dead	Typical

* All animals were sensitized subcutaneously with 0.05 c c human serum, April 6, 1921. Desensitizing doses in various amounts were given intravenously 28 days subsequently and the toxic doses the next day. Although in an attempt at homologous desensitization one animal succumbed to 0.05 c c serum, the toxic dose as determined the next day was 0.2 c c. Note the failure to protect of the smallest doses of heterologous serums.

experiment. The control animal which was not desensitized succumbed to 0.2 c c horse serum in 2 minutes and another given 0.1 c c survived. Desensitization with homologous horse serum showed symptoms in proportion to the size of the dose employed, but all survived. Of the desensitized animals all reacted severely following the shock dose, but it could not be noticed that there was much difference in reaction except that in a general way those desensitized with the larger doses of homologous horse serum were somewhat less severely shocked than those desensitized with smaller doses. Of 5 ani-

TABLE 6

The Effect of Intravenous Desensitization in Protection Against Double the Minimal Toxic Dose of Homologous Serum *

Animals		Desensitization			Intoxication				
No.	Wt. in Gm.	Serums and Amounts Intravenous, July 6, 1921		Reaction	Toxic Dose Horse Serum	Date	Hour	Reaction	Necropsy
76	325	—	—	—	0.2	7/7	11:14	11:15, rubbed nose, coughed, restless, mod. dysp.; 11:16, severe dyspnea; 11:18, urinated; 11:35, convulsions, on side; 12:10, dead	Moderate inflation of lungs
63	215	Horse	0.03	Moderate	0.5	7/7	3:30	3:32, moderate dyspnea	
168	295	Horse	0.03	Slight	0.5	7/7	3:28	Slight dyspnea	
318	300	Horse	0.03	Slight	0.5	7/7	3:25	3:26, rubbed head and nose; 3:26, mod. dyspnea; 3:27, severe dyspnea; 4:05, dead	Typical
379	220	Horse	0.03	Marked	0.5	7/7	3:22	3:20, slight to moderate dyspnea, hair ruffled, rubbed nose; 3:25, severe dyspnea	
146	290	Horse	0.01	Slight	0.5	7/7	3:20	3:21, rubbed nose, slight dyspnea	
178	300	Sheep	0.5	None	0.5	7/7	3:18	Coughed; 3:10, hair ruffled, convulsions; 3:20, on side; 3:27, dead	Typical
107	275	Sheep	0.5	None	0.5	7/7	3:16	3:17, scratched nose, hair ruffled, on side; dead at 4:30	Typical
34	200	Sheep	0.5	None	0.5	7/7	3:14	Coughed, rubbed nose; 3:16, moderate to severe dyspnea	
136	275	Sheep	0.3	None	0.5	7/7	3:09	3:10, restless, severe dyspnea	
71	275	Sheep	0.3	None	0.5	7/7	3:05	Coughed; 3:08, severe dyspnea, on side; 3:10, dead	Typical
176	280	Sheep	0.3	None	0.5	7/7	3:11	Hair ruffled; 3:12, rubbed nose and head; 3:15, on side; 4:00, dead	Marked inflation of lungs
180	350	Sheep	0.1	None	0.5	7/7	2:57	2:58, restless, scratched head, mod. dyspnea, hair ruffled	
286	225	Sheep	0.1	None	0.5	7/7	3:03	3:04, coughed, scratched nose, convulsions; 3:05, on side; 3:15, dead	Typical
310	330	Sheep	0.1	None	0.5	7/7	3:00	3:01, coughed, urinated defecated, severe dyspnea	

* All animals were sensitized with 0.05 c c horse serum, June 10, 1921. Desensitizing doses were given intravenously 26 days subsequently and double the minimal toxic dose the next day. In the amounts used there is little or no quantitative desensitizing effect demonstrated against the large intoxicating dose.

mals desensitized with human serum, all survived the subsequent shock dose. Of 5 animals desensitized with sheep serum one succumbed, namely, that which received 0.05 c c, next to the smallest dose for desensitization. The details of this experiment are essentially the same as those of the preceding experiment, and it is not considered necessary to append a protocol. All animals which received the smallest desensitizing doses reacted with distinctly greater severity than those receiving larger desensitizing doses except in the case of the fatality noted. The fact that the smallest doses in this series sufficed to protect, may be because the height of sensitization had passed, whereas in the preceding experiment it was maximal.

Series 9.—This series was undertaken in order to determine whether the protection afforded against a single minimal toxic dose would suffice to protect against a considerably increased toxic dose. In the control animal, not desensitized, death occurred 55 minutes after injection of 0.2 c c of homologous horse serum, but the animal reacted severely and promptly and death was delayed apparently only by marked individual resistance. Of those desensitized with homologous serum, one died following the large toxic dose of 0.05 c.c. Nine animals were desensitized with various doses of heterologous sheep serum. Five of these animals, a relatively high percentage, died with typical symptoms and with typical necropsy findings. Death occurred without any noticeable reference to the size of the desensitizing doses. It is probable that the differences in shock doses are not sufficiently marked to make any difference in response, or that all the doses employed are really maximal. Those animals which did not die had severe reaction regardless of whether the desensitization was with homologous or heterologous serums. As will be seen from table 6, the desensitizing doses of heterologous serums were approximately 10 times those of the homologous serum. As compared with other experiments, the doses in both the groups of animals were sufficiently large to insure adequate protection against a single toxic dose of the homologous serum, but it is apparent that with a larger toxic dose the protective effect of these doses is insufficient.

TABLE 7

THE EFFECT OF LAPSE OF VARIOUS TIME INTERVALS BETWEEN DESENSITIZATION AND INTOXICATION *

Number of Hours of Shock After Desensitization	Desensitization					
	Homologous Horse Serum		Heterologous			
			Human Serum		Sheep Serum	
	No. of Animals	Deaths	No. of Animals	Deaths	No. of Animals	Deaths
24	2	0	2	0	4	1
72	2	0	2	0	4	3
120	3	0	3	2	3	2

* All animals were sensitized subcutaneously with 0.05 c c horse serum, April 15, 1921. All were desensitized May 6, and shocked in groups May 7, 9 and 11.

Series 10.—This group of experiments was undertaken to determine the duration of desensitization by heterologous and homologous serums. The series comprises 32 animals and is too long for a detailed protocol. Table 7, however, gives a summary of the results. The animals were all desensitized on the same date with 0.05 c c homologous horse serum and 1 c c of the heterologous sheep and human serums. The animals were divided into groups and the members of each group were given the toxic dose of horse serum 24, 72 and 120 hours subsequently. The control animal, not desensitized, died following a dose of 0.12 c c homologous serum. According to the summary, all the animals that were desensitized with homologous serum survived. A large intravenous dose of sheep serum gave fairly adequate protection over the course of 24 hours, but after 72 and 120 hours the effect was greatly reduced. In the case of desensitization with human serum the effect was noticed for 72 hours after desensitization, but had almost disappeared at the end of 120 hours. An examination of the clinical symptoms manifested by the animals shows no important difference either as regards the length of time elapsed following desensitization or as regards the different serums used. The conclusion which may satisfactorily be drawn from this experiment is that heterologous desensitization is distinctly shorter in duration than is homologous desensitization.

DISCUSSION

A detailed statistical study of the experiments is subject to many factors of error, such as individual resistance or susceptibility of animals, the toxicity for guinea-pigs of some of the serums employed, and the relatively small number of animals in each series and in the entire group. The discussion of the experiments is therefore undertaken with a realization of its limitations. Although no exactly comparable experiments were made with intraperitoneal and subcutaneous methods of sensitization, no difference in effect is observed, and in view of preceding work on the subject it is safe to assume that the method of sensitization does not affect the attempts at desensitization.

A summary of the attempts at desensitization shows that of 5 animals desensitized by subcutaneous injection of homologous serums, none died as the result of the toxic dose. Of 19 animals desensitized subcutaneously by heterologous serums, 10 died. Following intraperitoneal desensitization with homologous serums, 1 of 6 animals died of the subsequently induced shock; with heterologous serums, 9 of 18 animals died. These figures do not indicate any practical advantage in the intraperitoneal as compared with the subcutaneous route. This result might well be altered in a larger series. Following intravenous desensitization with homologous serum, only 1 of 20 animals died of the subsequently induced shock, whereas with heterologous serums 20 of 56 animals died of subsequent shock. Including the total number of animals employed, it appears that intravenous desensitization with homologous serum is slightly superior to the subcutaneous or intraperitoneal routes. With the use of heterologous serum, the intravenous route is decidedly superior. Our examination of the question of multiple doses by the intraperitoneal or subcutaneous routes as contrasted with single doses is too small to be of service, but the work of Besredka and others leaves no doubt that multiple subcutaneous injections are superior to single subcutaneous injections. Our small series of 35 animals shows no superiority of multiple intraperitoneal injections over single injections by the same route. The number is too small, however, for accuracy or reliance.

Including all the series, it is found that of 31 animals desensitized with homologous serum only 2 died subsequently of anaphylactic shock. Of 93 animals desensitized with heterologous serums, 39 died of the subsequently produced shock. By the methods employed homologous desensitization is not necessarily prophylactic but gives, as will be seen from the preceding paragraph, apparently better results by the intravenous than by the subcutaneous or intraperitoneal routes. Heterologous desensitization saved more than half the animals in which it was employed. Here the intravenous method is decidedly superior; it shows 36% fatalities as compared with 51% fatalities by the intraperitoneal and subcutaneous routes.

It is apparent that a considerably larger quantity of heterologous serum than of homologous serum is required to protect. Preliminary experiments not reported in the protocols indicated that the ratio is approximately 10: 1, and it is for this reason that this ratio was employed in many of the experiments. In both homologous and heterologous desensitization, larger doses are more effective than very small doses, although this does not follow, as far as we can demonstrate, in any definite proportion. Protection is not so well assured against large intoxicating doses as against the minimal fatal dose. This lesser degree of protection is more evident in the case of heterologous, than of homologous, desensitization.

It is well known that the desensitized state in anaphylaxis is of comparatively short duration. The experiments in our last series indicate that the duration of protection is quite definitely shorter following heterologous than following homologous desensitization. It is true that symptoms of shock often appear as the result of homologous desensitization, whereas they are unusual following heterologous desensitization. If minor shock or shocks be the essential element of desensitization, then the reason for greater protection by homologous serums is apparent, but the fundamental nature of anaphylaxis is as yet unexplained and theories of desensitization must depend on a satisfactory explanation of the fundamental phenomena of sensitization and shock.

Antigenic antagonisms have been referred to in our review of the literature. Brack has shown that in highly sensitized animals actual shock may be produced by otherwise nontoxic heterologous serums, but is less marked than with the homologous serum. Lewis suggests that this phenomenon is due to a protein common to all the serums employed. It must be apparent, however, that the specificity of serum sensitization is not absolute, the specificity of serum anaphylactic shock is only relative, and the desensitized state may be produced by a wide variety of heterologous serums. Further studies are in progress with reference to the influence of colloidal disturbances on desensitization, but our present studies offer no explanation for the phenomena observed.

CONCLUSIONS

Animals sensitized to serum may be desensitized by the use of heterologous serums. The most effective desensitization is by the use of homologous serums.

Heterologous desensitization is most effective by the intravenous route. It develops with apparently the same rapidity as homologous desensitization but is of distinctly shorter duration.

Reactions appear in intoxicated animals following either form of desensitization, but are apparently somewhat less severe following homologous desensitization. The latter rule has many exceptions.

Heterologous desensitization becomes less effective as larger intoxicating doses of serum are used to produce shock. Homologous desensitization is more effective than heterologous in protection against large shock doses.